"Clinical outcome in patients treated with endoscopic submucosal dissection for superficial Barrett's neoplasia"

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Abstract

BACKGROUND AND STUDY AIMS: The role of endoscopic submucosal dissection (ESD) in Barrett's neoplasia is ill-defined, although it might provide a higher curative resection rate and better histologic assessment than endoscopic mucosal resection (EMR). We aimed to assess efficacy, safety, and long-term results of ESD. PATIENTS AND METHODS: A retrospective analysis was done of 75 consecutive patients with Barrett's esophagus who underwent ESD between January 2007 and February 2014.ESD was performed for visible lesions that were multiple, larger than 15mm, or poorly lifting, or suspected of submucosal infiltration. The primary end point was the rate of curative resection of carcinoma. RESULTS: Median patient age was 68 years (interquartile range [IQR] 61-76), median follow-up was 20 months (IQR 8.5-37.5), and median maximum specimen diameter was 52.5mm (IQR 43-71). En bloc resection rate was 90% (66/73), and rates of curative resection of carcinoma and hig...

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Clinical outcome in patients treated with endoscopic submucosal dissection for superficial Barrett's neoplasia

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Background and study aims: The role of endoscopic submucosal dissection (ESD) in Barrett's neoplasia is ill-defined, although it might provide a higher curative resection rate and better histologic assessment than endoscopic mucosal resection (EMR). We aimed to assess efficacy, safety, and long-term results of ESD.

Patients and methods: A retrospective analysis was done of 75 consecutive patients with Barrett's esophagus who underwent ESD between January 2007 and February 2014. ESD was performed for visible lesions that were multiple, larger than 15 mm, or poorly lifting, or suspected of submucosal infiltration. The primary end point was the rate of curative resection of carcinoma.

Results: Median patient age was 68 years (interquartile range [IQR] 61 – 76), median follow-up was 20 months (IQR 8.5 – 37.5), and median maximum specimen diameter was 52.5 mm (IQR 43 – 71). En bloc resection rate was 90 % (66 /73), and rates of curative resection of carcinoma and high grade dysplasia/carcinoma were 85 % (47 /55) and 64 % (42 /66), respectively. G3 differentiation and invasion to greater than pT1m2 were observed in 25 % (14 /55) and 67 % (37 /55) of patients with adenocarcinoma, respectively. There were 5 early (<48 hours) adverse events (2 delayed hemorrhages and 3 perforations), all treated endoscopically. No ESD-specific death occurred. Esophageal strictures developed in 60 % of patients, all treated endoscopically. Additional treatment (median sessions 2 [IQR 2 – 3]) for residual Barrett's esophagus were recommended to 62 % (42 /68). At latest follow-up, complete remission of neoplasia and intestinal metaplasia was found in 92 % (54 /59) and 73 % (43 /59) of patients, respectively.

Conclusion: ESD appears to be safe and effective, with a high rate of curative resection of carcinoma. ESD should be considered for patients with Barrett's neoplasia at risk of incomplete resection or poor pathologic assessment with conventional EMR.

Introduction

The worldwide burden of invasive esophageal adenocarcinoma (EAC), with records of its rising incidence and poor prognosis, has focused interest on Barrett's esophagus, a preneoplastic condition caused by gastroesophageal reflux disease [1,2]. The Barrett esophagus – EAC progression was first documented in the 1970 s, providing targets for the screening, monitoring, and endoscopic management of early-stage neoplasia. High grade dysplasia (HGD) and adenocarcinoma limited to the mucosa are the two indications for which endoscopic treatment is recommended [3, 4]. Based on the findings of Japanese studies pertaining to early-stage gastric neoplasia, European publications have suggested the existence of a submucosal EAC subtype (pT1bsm1) associated with a very low risk for lymph node metastasis [5,6]. For patients who have this particular subtype with low risk characteristics, recent guidelines have advised endoscopic excision as a valid alternative to esophagectomy [3,4].

The endoscopic management of Barrett's neoplasia consists of two steps [3]: first, the excision of endoscopically visible abnormalities for accurate diagnosis and staging [7,8], and second, eradication of the residual Barrett esophagus segment because of its metachronous lesion risk, which exceeds 20 % over a 2-year period [9]. Endoscopic mucosal resection (EMR) appears to be the treatment of choice for the excision procedure, with the advantages of being safe, effective, and the most comprehensively studied method [9 – 12]. In a prospective trial of EMR for mucosal cancer in 288 patients, complete responses were achieved in 97 % and 87 % of them after a median of 3 and 61 months, respectively [9]. No death

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related to Barrett's neoplasia was recorded at last follow-up [9]. This procedure, however, allows only piecemeal resection and is limited to lesions smaller than 15 mm. As for the eradication of residual Barrett's esophagus, several ablative techniques have been described [13 – 15], with radiofrequency ablation (RFA) currently considered the most effective method with the best side-effect profile [4, 16]. Nevertheless, this technique does not provide specimens for histopathologic evaluation, and the procedure is expensive and not reimbursed by national health systems in some countries. Stepwise radical endoscopic resection (SRER) has also been suggested, although strictures occur in half of the patients [17, 18].

Endoscopic submucosal dissection (ESD) has recently emerged as a potential technique to improve complete resection rates. In a meta-analysis, ESD was shown to achieve better rates of en bloc and curative resection and less local recurrence of gastrointestinal tract tumors compared with EMR [19]. ESD should therefore be the preferred technique because it provides the most reliable histopathologic assessment for accurate staging. Moreover, this technique potentially enables the endoscopic treatment of challenging lesions, such as those that are nonlifting, measure more than 20 mm, or are suspected of deep mucosal invasion. On the other hand, ESD is more time-consuming and associated with more serious complications than the other techniques, so that expertise and experience are required [19, 20].

This study sought to assess the efficacy, safety, and long-term results of ESD in neoplasia associated with Barrett's esophagus in a large number of patients referred to a tertiary center.

Patients and methods

Patients

Our study selected patients from a prospective registry of more than 300 patients treated with endoscopic resection or ablation (RFA, argon plasma coagulation [APC]) of Barrett's neoplasia and followed in our department between January 2007 and February 2014. Indications for ESD were as follows:

1. Barrett's esophagus containing HGD or superficial EAC;
2. visible lesions (Paris classification 0-I/II [21]) that were multiple, measured more than 15 mm, were poorly lifting (no rise after submucosal injection or no rise during suction with the multiband mucosectomy [MBM] cap), or were suspected of submucosal infiltration (T1sm1) at endoscopy or endoscopic ultrasonography;
3. no sign of deeper invasion (> sm2 or T2); and
4. no sign of metastatic disease on endoscopic ultrasonography or computed tomography.

ESD was done only when all of these criteria were met. EMR or ablation techniques were offered to the other patients. Only charts from patients treated with ESD were retrospectively analyzed. The following clinical variables were collected in the ESD cohort and reviewed: patient age at the time of diagnosis of Barrett esophagus and ESD procedure; patient sex; risk factors for nonlifting lesions (previous Barrett esophagus-related endoscopic resection, esophageal surgery, or radiotherapy); risk factors for complications (strictures, portal hypertension, or anticoagulation); and proton pump inhibitor (PPI) use. The study was approved by the Faculty of Medicine's ethics committee and institutional review board. Before each ESD procedure, written informed consent was obtained.

Procedures

All ESD procedures were carried out by three experienced operators (P.H.D., H.P., and R.Y.). An anesthesiologist administered deep sedation with a continuous intravenous propofol infusion during all endoscopic procedures, along with tracheal intubation. Carbon dioxide insufflation was routinely used. We employed high resolution video endoscopes with white light and narrow-band imaging (GIF-H180, GIF-H190, or GIF-HQ190; Olympus Medical Systems, Tokyo, Japan) for detailed Barrett esophagus evaluation. Circumferential and maximum extent of Barrett esophagus were

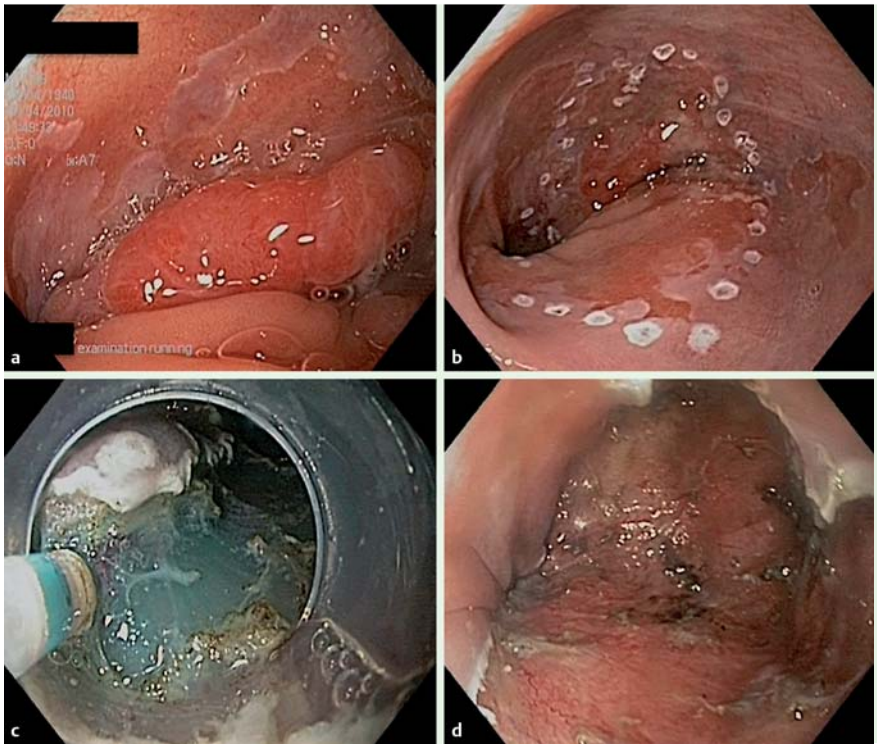

Fig. 1 En bloc and curative resection with endoscopic submucosal dissection in a 60-year-old patient with carcinoma-associated Barrett's esophagus. **a** Endoscopic view of C2 M3 Barrett's esophagus with a 2-cm lesion, Paris classification 0-IIa. **b** Coagulation markings around the suspected lateral margin of the neoplastic area with a safety margin. **c** Dissection of the submucosa with a DualKnife. **d** Resection area after dissection and hemostasis.

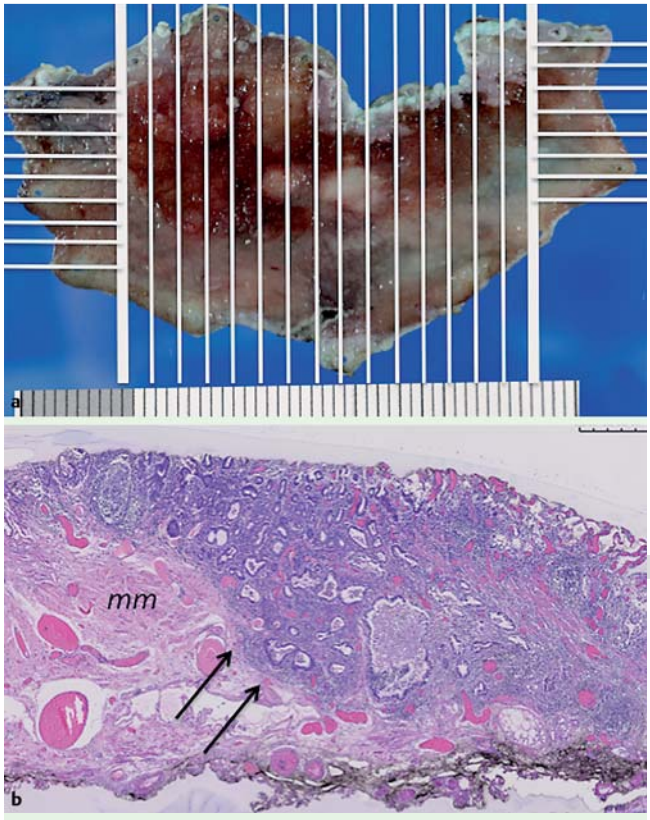

Fig. 2 Same patient as **Fig. 1a** Macroscopic view of en bloc specimen measuring 5.6 × 3.6 cm shows two central brownish lesions; white lines indicate axis of cut. **b** Histologic appearance shows an esophageal adenocarcinoma with limited invasion of the submucosa (black arrows) and with free vertical and horizontal margins. Final diagnosis and staging: pT1sm1, G1, L–, V–. mm, muscularis mucosae.

described according to the Prague classification [22]. The size and type of visible defects were reported according to the Paris endoscopic classification [21].

The type of ESD knife used for the procedures was recorded. The knife tip was used in soft coagulation mode to delineate the edge of the endoscopic resection area, with a 3 – to 5-mm safety margin (**Fig. 1**). The mucosa was lifted by means of a submucosal injection of 30 % gelatin (Geloplasma, 500 mL mixed with 1 mg of epinephrine and 1 mL of methylene blue for staining; Fresenius Kabi, Schelle, Belgium). Incision and dissection were performed in the endocut and swift coagulation modes, respectively (Vio 300; ERBE, Diegem, Belgium). Hemostasis was achieved with either the knife tip or a Coagrasper (Olympus Belgium, Aartselaar, Belgium) in soft coagulation mode. Once the specimen was extracted, all residual superficial and perforating vessels were coagulated. We recorded the procedure duration time, endoscopic resection circumferential diameter, use of complementary endoscopic techniques (EMR, APC), and post-procedural oral corticosteroid therapy. ESD failure was defined as failure to achieve complete resection with ESD because of strong adherence with no safe dissection plane, uncontrollable bleeding, or perforation. Full resection of the neoplasia and surrounding Barrett esophagus was attempted in a single session if the Barrett mucosa was not circumferential.

Adverse events

Adverse events were defined as early (< 48 hours) or late (> 48 hours). Procedural bleeding that could be managed endoscopically with the knife, hemostatic forceps, or hemoclips was not considered a complication. Major procedural bleeding that was unmanageable by endoscopic means and delayed bleeding that required endoscopic re-evaluation or red blood cell transfusion were considered adverse events. Perforation was defined as a visible hole in the esophageal wall or radiologic evidence of collected extramural fluid. A stricture was determined to be present when it was difficult or impossible to pass a gastroscope through the resection area at 2 weeks or more following ESD.

Histopathologic evaluation of resected specimens

Each specimen was pinned down with needles immediately after removal and fixed in formalin for 24 hours. If en bloc resection had not been achieved, an attempt was made to reconstruct the topography of the specimen. Photographs were taken of the fixed specimen and recorded. The deep and lateral resection margins of all specimens were marked with black India ink. Specimen number and maximum diameter were noted. Following these steps, the specimens were cut at 2-mm intervals into strips perpendicular to the main axis and along the main axis near the borders in order to assess the lateral margins precisely (**Fig. 2**). The sections were serially placed into cassettes, routinely processed, and stained with hematoxylin and eosin.

The assessment was carried out by a senior pathologist experienced in EAC diagnosis (A.J.-M.). Histopathologic reports were recorded in accordance with the Vienna classification [23] and Japanese recommendations [24]. We evaluated presence of intestinal metaplasia, size, depth of invasion, and grade of differentiation (G). Vertical and horizontal margin status was assessed according to neoplasia determination: margins free of carcinoma, high grade intraepithelial neoplasia, or low grade intraepithelial neoplasia (R0), or margins infiltrated with neoplasia (R1). D2 – 40 immunohistochemistry was used to assess for lymphatic invasion, and in all cases with submucosal invasion or G3 adenocarcinoma [25].

Follow-up

Patients were hospitalized for 24 hours following ESD and underwent a PPI regimen at triple (3 × 40 mg) the standard dose until the mucosa was completely healed. If the esophagogram revealed no leakage of contrast, patients were discharged on the day following ESD. Endoscopic follow-up was scheduled at 2 weeks for all patients, to check for postoperative stricture and initiate a preventive dilation program. In the event of increasing dysphagia or lumen narrowing, repeated dilations with controlled radial expansion balloon dilators (Boston Scientific, Diegem, Belgium) were done every week and repeated until dysphagia resolution. When refractory strictures (more than four dilations without significant improvement) were observed, self-expandable stent placement was considered.

When necessary, subsequent treatments aimed at removing residual Barrett esophagus were administered during follow-up endoscopic procedures at 6, 12, and 18 months, then yearly if residual Barrett's mucosa was still observed. These procedures took into account patient age, co-morbidities, and willingness to continue endoscopic treatment; they were discontinued when the mucosa had completely healed and in the absence of significant stricture. High resolution video endoscopy, combined with narrow band imaging (NBI) and chromoendoscopy with 2 % acetic

acid staining, was used to carefully examine the esophageal scar and mucosa. Targeted biopsy specimens were extracted from both the columnar epithelium areas and random areas just underneath the neo-squamocolumnar junction (neo-SCJ). For patients who were followed up by their referring endoscopists, all endoscopy and histopathologic reports were requested. Surgery or chemoradiotherapy was considered in the event of noncurative endoscopic treatment in accordance with locally established criteria of good clinical practice. When surgery was deemed necessary, all histopathologic reports were requested.

End points

The rate of curative resection of carcinoma, which was defined as a histologically complete resection of carcinoma in ESD specimens, along with horizontal and vertical margins negative for adenocarcinoma and the absence of lymphatic (L) and venous (V) invasion, was the primary end point.

Secondary end points were as follows:

- rate of en bloc resection (excision of the neoplastic lesion in a single specimen);
- rate of curative resection of high grade neoplasia and carcinoma, defined as histologically complete excision with horizontal margins free of HGD;
- rate of curative resection of neoplasia, defined as histologically complete excision with horizontal margins free of any low grade or high grade dysplasia;
- number of adverse events;
- number of sessions of additional therapy required following the first ESD;
- rate of complete remission of neoplasia, defined as the absence of high grade neoplasia or carcinoma in biopsy specimens taken from the esophageal mucosa and from an area immediately distal to the neo-SCJ at most recent follow-up; and
- rate of complete remission of intestinal metaplasia, defined as the endoscopic eradication of Barrett's esophagus associated with absence of intestinal metaplasia in biopsy specimens taken from the esophageal mucosa and from an area immediately distal to the neo-SCJ at the end of the eradication program.

Statistical analysis

Quantitative variables were presented as median and interquartile range (IQR). Proportions were expressed as percentages.

Results

Baseline characteristics

The study included 75 consecutive patients. The median age of the patients was 68 years (IQR 61 – 76), and 63 patients were male (85 %) (**Table 1**). A total of 22 patients had risk factors for nonlifting lesions, such as previous endoscopic treatment (17 %), esophageal surgery (11 %), and radiotherapy (1.3 %). Most patients (93 %) were following a PPI regimen at the time of ESD. Median time between Barrett's esophagus diagnosis and ESD was 41 months (IQR 11 – 190), with a median maximum segment length of 6 cm (IQR 4 – 9). The median maximum diameter of a visible lesion was 20 mm (IQR 10 – 30), and the main lesion types encountered were classified as 0-IIa (55.7 %) and 0-IIc (36 %) according to the Paris endoscopic classification.

Table 1 Baseline characteristics of 75 patients undergoing endoscopic submucosal dissection (ESD) for superficial Barrett's neoplasia.

Clinical characteristics	
Patient age at ESD procedure, median (IQR), y	68 (61 – 76)
Sex ratio, M/F	5.25
Past medical history, n (%)	
Cirrhosis	4 (5)
Previous esophageal surgery	8 (11)
Previous esophageal radiotherapy	1 (1.3)
Previous endoscopic treatment	13 (17)
PPI treatment, n (%)	70 (93)
Endoscopic characteristics	
Hiatal hernia, n (%)	50 (67)
Barrett's duration, median (IQR), mo	41 (11 – 190)
Barrett's length, median (IQR), cm	
Circumferential extent	2.5 (1 – 6.75)
Maximum segment length	6 (4 – 9)
Neoplastic lesion characteristics	
Visible lesions, n (%)	70 (93)
Maximum diameter, median (IQR), mm	20 (10 – 30)
Paris classification (70 patients), n (%)	
0-Ip	1 (1.4)
0-Is,	1 (1.4)
0-IIa,	39 (55.7)
0-IIb,	4 (5.7)
0-IIc	25 (36)

IQR, interquartile range; PPI, proton pump inhibitor.

Table 2 Procedure characteristics and adverse events in 75 patients undergoing endoscopic submucosal dissection (ESD) for superficial Barrett's neoplasia.

Procedure	
Procedure duration, median (IQR), min	117 (100 – 145)
ESD failure, n (%)	2 (2.5)
ESD device used, %	
DualKnife	76
FlexKnife	19
IT Knife	11
Nestis	1
HybridKnife	4
Complementary endoscopic resection technique, n (%)	
Total patients	9 (12)
EMR,	5 (7)
APC,	3 (4)
EMR + APC,	1 (1)
En bloc resection, n/n (%)	66 /73 (90)
Circumferential extent, median (IQR), %	75 (66 – 80)
Oral corticosteroids after procedure, n, %	13 (17)
Complications, n (%)	
Early (< 48 h)	
Bleeding	2 (2.7)
Perforation,	3 (4)
Late (> 48 h)	
Bleeding,	0 (0)
Perforation,	0 (0)
Strictures,	45 (60)
30-day mortality	0 (0)

IQR, interquartile range; EMR, endoscopic mucosal resection; APC, argon plasma coagulation.

ESD successful resection	
Patients, n	73
Maximum specimen diameter, median (IQR), mm	52.5 (43 – 71)
	1 (1.4)
Neoplasia findings	
Intestinal metaplasia only, no neoplasia, n/n (%)	1/73 (1.4)
Patients with neoplasia, n/n (%)	72/73 (98.6)
Low grade dysplasia (LGD), n/n (% of patients with neoplasia)	6/72 (8.3)
High grade dysplasia (HGD), n/n (% patients with neoplasia)	11/72 (15.3)
Esophageal adenocarcinoma (EAC), n/n (% patients with neoplasia)	55/72 (76.4)
EAC	
Total, n	55
Grade of differentiation, n/n (% of EACs)	
G1	31/55 (56.4)
G2	10/55 (18)
G3	14/55 (25.6)
Depth of invasion, n/n (% of EACs)	
pT1 m2	18/55 (32.7)
pT1 m3	30/55 (54.5)
pT1 sm1	6/55 (11)
pT1 sm2	0/55 (0)
pT1 sm3	1/55 (1.8)
Lymphatic/vessel invasion, n (% of EACs)	1/55 (1.8)
Resection rates, n/n (%)	
Curative resection of carcinoma	47/55 (85)
Curative resection of HGD/carcinoma	42/66 (64)
Curative resection of neoplasia (CRN)	40/72 (56)
Incomplete resection of neoplasia	
At lateral margin	27/72 (38)
At deep (vertical) margin	6/55 (11)

IQR, interquartile range.

Table 3 Histopathological results for endoscopic submucosal dissection (ESD) specimens.

Procedural characteristics

The median procedure time for ESD was 117 minutes (IQR 100 – 145), including lesion inspection, dissection, coagulation of all visible vessels, and perforation closure when necessary (**Table 2**). En bloc resection was achieved in 90% of ESD procedures. ESD was not possible in 2 of the 75 patients because of a nonlifting lesion with abundant sites of hemorrhage in one, who had liver cirrhosis, and because of a perforation, treated endoscopically, in the other.

The majority of ESD procedures (76%) were done with the Dual-Knife (KD-650Q; Olympus Belgium).

Complementary EMR and/or APC was used in 9 ESD procedures, for the treatment of smaller synchronous lesions or to complete eradication of Barrett esophagus (isolated islets of Barrett's mucosa). Following the ESD procedure, to prevent strictures 13 patients (17%) were administered an oral corticosteroid regimen that was slowly tapered. This regimen was proposed from the end of 2012 in patients with circumferential excision and in selected patients (for example, with previous stricture or eosinophilic esophagitis).

Histopathologic outcomes

Of the 73 patients whose ESD was successful, the histology of the resected specimen revealed intestinal metaplasia with neoplasia in 98.6% of cases (72/73), with associated EAC in 76.4% (55/72) (**Table 3**). The EACs were limited primarily to the mucosa (87.2%, 48/55), with 6 revealed to have invaded the submucosal layer to less than 500 µm (sm1). On definitive histopathologic evaluation, 30 and 6 flat (Paris 0-II) lesions presented as with pT1m3 and pT1sm1 adenocarcinomas, respectively,. Of the 6 pT1sm1 lesions, 3 exhibited low risk characteristics, as previously described (G1/G2, R0, L0, V0), whereas the other 3 were lesions with undifferentiated nests. Only 1 lesion, which was classified as stage pT1m3 with G3 differentiation, exhibited infiltration of the lymphatic and/or venous vessels.

The primary end point of curative resection of carcinoma was attained in 85% (47/55) of patients. Failure of curative resection of carcinoma was observed among patients with lesions classified as having G3 differentiation (n=7) and/or positive vertical (deep) margins (n=6). Curative resection of neoplasia was observed in 56% (40/72) of the histopathologic specimens (**Fig. 3**).

Adverse events

No major intraprocedural bleeding occurred (**Table 2**). Despite having carried out meticulous coagulation of all visible vessels, we observed 2 patients (2.5%) with delayed bleeding in the first 48 hours, both treated endoscopically. No red blood cell transfusion was required. The bleeding occurred in patients without risk factors such as cirrhosis, anticoagulant or antiplatelet drug intake, or hemopathy. Of the 3 perforations recorded (4%), 2 occurred during the ESD procedures, one of which had to be discontinued (ESD failure), and the third was diagnosed by esophagography 24 hours after the ESD procedure. All perforations were treated endoscopically, 2 with fully covered self-expandable stents (WallFlex; Boston Scientific, Diegem, Belgium) and the third with endoclips (EZClip; Olympus Belgium). No mediastinitis was observed, and the clinical evolution was favorable. We recorded no further related complications during hospitalization.

Esophageal strictures were the only late complications, observed in 60% (n=45) of patients. All were treated with a median number of 4 sessions of endoscopic balloon dilation (IQR 2 – 6). In ad-

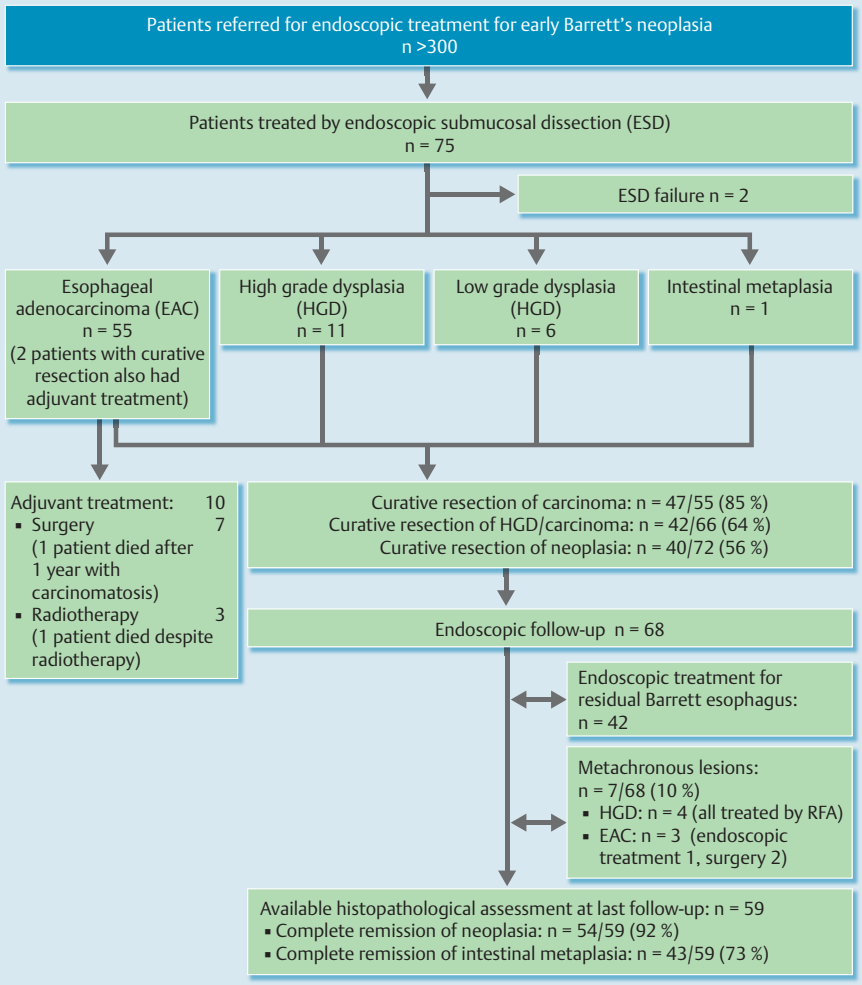

Fig. 3 Endoscopic submucosal dissection (ESD) in patients with superficial Barrett's neoplasia: study flowchart. HGD, high grade dysplasia; RFA, radiofrequency ablation.

dition, 6 stents were placed, and other techniques, such as bougie dilation, triamcinolone injection, and radial incision, were also used.

All complications were managed endoscopically, and no ESD-specific death was reported.

Follow-up

The median hospitalization stay was 2 days (**Table 4**), and the median follow-up period was 20 months (IQR 8.5 – 37.5).

Adjuvant treatment was proposed to 10 patients, based on locally established criteria of good clinical practice, with 7 eventually undergoing surgery (**Table 5**). Surgery was mandatory for 5 patients because of infiltrated margins or defined G3 differentiation with submucosal involvement (**Table 5**). The 2 patients who had pT1sm1 EAC with low risk characteristics underwent surgery in 2010 and 2011, respectively; definitive histology revealed neither neoplasia nor positive lymph nodes. The last 3 patients could not undergo surgery because of their age at the time of procedure (2 of them were 90 years old) and co-morbidities. Radiotherapy was then performed without chemotherapy because of their performance status. At the most recent follow-up, 2 of those 3 patients were still alive and exhibited no recurrence.

Overall and disease-specific mortality rates were therefore 8 % (n = 6) and 2.7 % (n = 2), respectively. The first disease-specific death was of a 90-year-old woman, one of the last 3 patients mentioned above, who presented with undifferentiated EAC (G3, pT1m3) and infiltrated lateral margins which could not be operated on. Radiotherapy was unsuccessful. The second disease-specific death was in a patient who had surgery for a poorly differentiated EAC (G3, pT1sm1) also with infiltrated vertical (deep) margins. This patient died 1 year later of carcinomatosis despite surgical treatment.

Additional treatment methods for residual Barrett's esophagus were proposed to 62 % of patients (42 of 68 with endoscopic follow-up), with a median of 2 sessions (IQR 2 – 3). RFA was the most frequently used technique for eradication (50 %, 21 out of 42 patients). ESD, APC, and EMR were also used in 36 % (15 /42), 36 % (15/42), and 29 % (12/42), of the patients, respectively. There were 3 patients who required fundoplication surgery owing to persistent peptic esophagitis despite PPI dose escalation up to 240 mg/d. At the most recent endoscopic follow-up, complete eradication of HGD or EAC had been achieved in 54 of 59 patients (92 %). Of the 5 patients exhibiting persistent HGD or EAC at the latest follow-up, 4 were still alive, 2 were referred for surgery, and 2 were still undergoing RFA treatment. As for complete remission of -intestinal metaplasia, 43 of 59 patients (73 %) showed endoscopic and histologic eradication of intestinal metaplasia at the end of the eradication program, with additional treatment used when required.

We have recorded 7 metachronous lesions, defined as high grade intraepithelial neoplasia or carcinoma detected after 2 negative follow-up sessions of high resolution endoscopy with systematic biopsies (**Table 4**). Of these, 4 lesions consisted of HGD, all managed with RFA (1 still being treated). The other 3 lesions

Table 4 Clinical, endoscopic, and histologic follow-up of patients who underwent endoscopic submucosal dissection (ESD) for superficial Barrett's neoplasia.

Clinical course	
Patients, n	75
Hospitalization duration, median (IQR), d	2 (2 – 2)
Follow-up duration, median (IQR), mo	20 (8.5 – 37.5)
Endoscopic follow-up, n (%)	68 (91)
Surgery, n (%)	9 (12)
Radiotherapy, n (%)	3 (4)
Overall mortality, n (%)	6 (8)
Disease-specific mortality, n (%)	2 (2.7)
Endoscopic follow-up	
Patients, n	68
Residual Barrett's esophagus	
Patients treated for residual Barrett's, n/n (%)	42/68 (62)
Sessions for eradication of residual Barrett's, median (IQR), n	2 (2 – 3)
Endoscopic technique used, n/n (%)	
EMR	12/42 (29)
ESD	15/42 (36)
APC	15/42 (36)
RFA	21/42 (50)
Metachronous lesions, n (%)	7/68 (10)
HGD	4
Esophageal adenocarcinoma (EAC)	3
Histopathologic follow-up	
Patients, n	59
Complete remission of neoplasia, n/n (%)	54/59 (92)
Complete remission of intestinal metaplasia, n/n (%)	43/59 (73)

IQR, interquartile range; EMR, endoscopic mucosal resection; APC, argon plasma coagulation; RFA, radiofrequency ablation; HGD, high grade dysplasia.

were EAC, 2 treated surgically and 1 managed endoscopically. The decision to operate was made by referring physicians.

Discussion

Few data are available on ESD in Barrett's neoplasia [26 – 29]. In Western countries, the high safety and success rates of EMR are offset by technical difficulties and the risk of ESD to the esophagus [30, 31]. In Asian countries, Barrett's esophagus is an uncommon condition, and adenocarcinoma is still rare [32]. For these reasons, EMR is the gold standard in current clinical practice for endoscopic excision in Barrett's neoplasia. The main limitation of EMR is the piecemeal nature of the resection that is usually required, which hampers histopathologic assessment and curative resection based on "oncology standards," with en bloc resection and free margins [33]. In a recent meta-analysis and systematic review, higher rates of en bloc and curative resection were reported for ESD than for EMR, irrespective of lesion size [19, 20]. In our study, en bloc resection was achieved in 90% of patients with successful ESD, and curative resection of carcinoma in 85% of patients (47/55) presenting with superficial carcinoma. Curative resection of carcinoma is rarely achieved with the EMR technique because of the piecemeal nature of the resection. In a prospective study of 100 patients with Barrett's neoplasia, curative resection of carcinoma was achieved in 33% of EMR procedures, even though lesion diameters were less than 20 mm [10]. Our results have confirmed the superiority of ESD over EMR for en bloc and curative resection of carcinoma.

It is difficult to find an assessment of the ESD technique for Barrett's neoplasia in the scientific literature, as most available esophageal ESD data focus on squamous cell carcinoma or esophagogastric junction adenocarcinoma [26, 28, 34, 35]. Moreover, definitions of complete and curative resection differ slightly among studies. ESD efficacy in this particular situation has been evaluated in three studies: a prospective trial from Germany [27] and one prospective [28] and one retrospective study [36] from Japan involving 30, 25, and 23 patients, respectively. Complete resection was achieved in 38.5%, 64%, and 85% of patients in these studies, respectively [27, 28, 36]. The reason for incomplete resection of neoplasia in patients who did not undergo surgery was the presence of systematically infiltrated lateral margins, which were difficult to recognize before endoscopic treatment. These data underscore the need for more advanced imaging techniques to assess Barrett's neoplasia before and during endoscopic treatment [37]. Furthermore, a recent study reported a subsquamous extension of intestinal metaplasia in 98% of patients with this condition [38]. The authors consequently advised that any resection of neoplastic Barrett's esophagus should extend for at least 1 cm into the squamous epithelium [38]. In our study, markings were usually placed 3 mm outside the lesions, and the resection aimed to excise the lesion and all the markings. This may account for the higher rate of curative resection of carcinoma (85%) observed in our patients, with larger specimens resected (median 52.5 mm), although with an unfortunately higher stricture rate owing to the greater circumferential extent of excision (median 75%).

One unexpected finding in our study was the high G3 rate, observed in 25% of patients with adenocarcinomas, along with the deep invasion rate, to more than pT1m2 in 67% (37/55) of cases. This finding may be due either to the case selection process (large visible lesions and referral center for ESD) or to an improved pathologic assessment in en bloc resections. Indeed, a piecemeal resection of mucosal carcinoma may lead to the understaging of deeper invasion or nests of undifferentiated cancer [39]. Even flat (Paris 0-II) lesions were revealed to harbor carcinoma that invaded the muscularis mucosae, which might not be properly assessed histologically in a piecemeal fashion. In addition, 7 patients (9%) were given a diagnosis of submucosal carcinoma. Of these, 3 exhibited low risk characteristics (R0, L0, V0, G1/G2) [5, 40], 2 of whom underwent surgery, with no residual neoplasia reported on post-surgical histopathology. The third patient underwent endoscopic surveillance, with no recurrence reported at latest follow-up. The 4 other patients presented with high risk lesions (G3 and/or positive vertical [deep] margin), yet post-surgical histopathology revealed no residual carcinoma for 2 of them. One patient died of post-surgical complications, reminding us of the higher mortality risk for surgical candidates.

To prevent metachronous lesions, additional eradication techniques have been recommended in the context of residual Barrett's esophagus. The lower curative resection rate for dysplasia observed in our study (64% when only HGD is considered and 56% when both low and high grade dysplasia are considered at the horizontal margins) confirmed the frequent presence of adjacent intraepithelial neoplasia in the remaining Barrett's mucosa. Additional treatment, consisting primarily of RFA, was therefore advised for a large proportion of our patients (65%, 44/68), with their age, co-morbidities, and willingness to pursue treatment taken into account. At the end of the eradication program, complete endoscopic eradication of Barrett's esophagus with no intestinal metaplasia was achieved in 73% of patients (43/59).

Table 5 Adjuvant surgery or chemotherapy in 10 patients following endoscopic submucosal dissection (ESD) for superficial Barrett's neoplasia: treatment and subsequent histopathology results.

Patient no.	Age, y, sex	Specimen size, mm	Histopathology findings			Adjuvant treatment Histopathologic evaluation/ Outcomes
			Lesion classification	Lateral margin	Deep (vertical) margin	
1	66, M	44	EAC pT1sm3, G2, L0, V0	R0	R1	Abdominothoracic esophageal resection Intestinal metaplasia +, HGD +, N0 No recurrence at last follow-up
2	72, M	35	EAC pT1 sm1, G3, L0, V0	R0	R1	Abdominothoracic esophageal resection pT1m3, intestinal metaplasia +, HGD +, N0 Post-surgery death
3	70, M	56	EAC pT1sm1, G1, L0, V0	R0	R0	Abdominothoracic esophageal resection Intestinal metaplasia +, N0 No recurrence at last follow-up
4	59, M	38	EAC pT1sm1, G2, L0, V0	R0	R0	Abdominothoracic esophageal resection No tumor, N0 No recurrence at last follow-up
5	68, M	57	EAC pT1sm1, G3, L0, V0	R0	R1	Abdominothoracic esophageal resection pT1sm1, G3, intestinal metaplasia +, LGD +, HGD +, N1 Carcinomatosis and death 1 year later
6	67,, M	65	EAC pT1sm1, G3, L0, V0	R0	R1	Abdominothoracic esophageal resection HGD +, N0 No recurrence at last follow-up
7	54, M	65	EAC pT1m3, G3, L0, V0	R0	R1	Abdominothoracic esophageal resection Intestinal metaplasia +, N0 No recurrence at last follow-up
8	90, F	40	EAC pT1m3, G3, L0, V0	R0	R1	Inoperable patient, radiotherapy Carcinomatosis and death 1 year later
9	90, M	32	EAC pT1m3, G3, L0, V0	R1	R0	Inoperable patient, radiotherapy No recurrence at last follow-up
10	75, M	45	EAC pT1m3, G3, L +, V0	R0	R0	Inoperable patient, radiotherapy No recurrence at last follow-up

M, male; F, female; EAC, esophageal adenocarcinoma; L, lymphatic invasion; N, lymph node; V, venous invasion; HGD, high grade dysplasia; LGD, low grade dysplasia; +, present

These results were similar to those published in the recent scientific literature, especially in light of the long-segment Barrett's esophagus treated in our cases (median maximum segment length 6 cm, IQR 4 – 9). In a meta-analysis that assessed the efficacy of RFA in Barrett's esophagus eradication, complete eradication of intestinal metaplasia was achieved in 78 % of patients (95 %CI 70 % – 86 %) [41]. In a systematic review of 22 studies aimed at comparing the RFA and EMR techniques, the success of eradication of intestinal metaplasia was variable across studies, ranging from 55 % to 100 % following RFA, and from 80 % to 96 % following complete EMR [42].

During follow-up, 7 metachronous neoplastic lesions (HGD/EAC) appeared. In a retrospective study by Pech et al. involving 279 patients with EMR, metachronous lesions were found in 74 patients (26.5 %) during follow-up [9]. Piecemeal resection was the main risk factor associated with recurrence [9]. Other risk factors consisted of long-segment Barrett's esophagus, time until complete local remission longer than 10 months, multifocal neoplasia, and no ablative therapy of Barrett's esophagus following complete local excision [9]. The risk for recurrent lesions in the digestive tract was significantly higher with EMR than with ESD in a recent meta-analysis and systematic review [19, 20]. This has been confirmed by our results, with metachronous lesions reported in 9 % of patients, all treatable endoscopically or by surgery. However, no conclusion in terms of metachronous lesion occurrence could be drawn from our results compared with those of Pech et al. because their follow-up was longer (63 months), and EMR was not the only endoscopic treatment for the resection of Barrett's neoplasia [9].

In our study, 5 early complications occurred (6.7 %, among 75 patients), which were all managed endoscopically. In the German and Japanese studies, the rate of early complications varied between 6.6 % and 4 % [27, 28]. These rates were similar to those previously described with the EMR technique [9, 10, 43]. This relative safety was offset by the rate of esophageal strictures, occurring in more than half of patients, which is higher than rates previously described with EMR (0 % – 25 %), and strictures can hamper quality of life [10, 44]. However, in the SRER approach, strictures were also observed in more than 50 % of patients [17, 45]. Ono et al. analyzed predictors of postoperative stricture following 11 ESD procedures for superficial squamous cell carcinoma [46]. In a multivariate analysis, circumferential extent involving more than 75 % of the whole lumen and invasion depth to greater than pT1m2 were significantly associated with stricture occurrence [46]. Tumor size (> 59 % of the circumference) was also thought potentially to be involved [47]. In our study, the median circumferential extent of resection was 75 %, and invasion depth was to greater than pT1m2 in more than 60 % of patients, two factors that may explain the high stricture rate observed in our patients. In addition, approximately one-third of patients had undergone previous esophageal surgery, radiotherapy, or endoscopic treatment, which might have facilitated fibrosis formation. Oral or topical corticosteroids can reduce the need for dilation and prevent stricture occurrence, as shown in recent studies

[46,48]. Although some of our patients are now receiving treatment with oral corticosteroids, their clinical benefit is still under investigation.

The median procedure duration was 117 minutes, which is longer than that reported with EMR and in previous ESD studies [27, 28]. Performing ESD in the Barrett's mucosa or near the esophagogastric junction can prove difficult owing to fibrosis, possible hiatal hernia, or previous treatment [49]. A recent report from Japan reported a median procedure duration of 95 minutes (range 30 – 210 minutes) for lesions with a median tumor size of 15 mm (range 5 – 60 mm) [36]. The difference seen in our study might be accounted for by our larger specimen sizes (52.5 mm, IQR 43 – 71) and the fact that our procedure duration included not only the dissection but also all the other ESD steps, namely, inspection, marking, incision, dissection, meticulous coagulation, and perforation closure when necessary.

The main limitations of this study were its retrospective and uncontrolled design, as it was conducted in a single tertiary center with comprehensive experience in ESD and Barrett's neoplasia. Our reported safety and efficacy rates may therefore differ from those of centers where ESD is practiced less frequently. Besides, because of its retrospective and uncontrolled design, the study may suffer from selection and inclusion bias.

In summary, this is the largest series of ESD for Barrett-associated superficial neoplasia. ESD appears to be safe and effective in an experienced center, with a high rate of curative resection of carcinoma. Based on our results, ESD should be considered in selected patients, such those with lesions larger than 15 mm, poorly lifting tumors, or lesions at risk for submucosal invasion. Indeed, an en bloc resection may provide a better histologic evaluation of some lesions, such as those with deeper invasion (> pT1m2) or G3 differentiation, as they were more frequently observed in our patients than in patients in previous EMR trials. Because ESD has not been shown to be superior to EMR for the excision of mucosal cancer, multicenter randomized controlled trials are needed to define the role of ESD compared with EMR. The high rate of esophageal stenosis is a major drawback of extensive endoscopic resection, including ESD, and techniques to prevent post-ESD strictures should be investigated further.

Competing interests: None

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